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**Metabolic Syndrome, Insulin Resistance and Cognitive Dysfunction: Does your
metabolic profile affect your brain?**

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1 Abstract

2 Dementia and type 2 diabetes are both characterized by long prodromal phases challenging the study of
3 potential risk factors and their temporal relation. The progressive relation between metabolic syndrome,
4 insulin resistance, and dementia has recently been questioned, wherefore the aim of this study was to
5 assess the potential association between these precursors of type 2 diabetes and cognitive dysfunction.
6 Using data from the Prospective Epidemiological Risk Factor study (n=2,103), a prospective study of
7 elderly women in Denmark, we found that impaired fasting plasma glucose was associated with 44%
8 (9%-91%) larger probability of developing cognitive dysfunction. In addition subjects above the
9 HOMA-IR threshold (HOMA-IR > 2.6) had 47% (9%-99%) larger odds of cognitive dysfunction. The
10 associations could indicate that a significant proportion of dementia cases in women is likely to be
11 preventable by effective prevention and control of the insulin homeostasis.

12

1 The sedentary western life-style has led to an epidemic-like increase in prevalence of obesity that is
2 closely linked to occurrence of type 2 diabetes (1,2). Also the prevalence of cognitive dysfunction and
3 dementia is increasing and epidemiological studies suggest an association between type 2 diabetes and
4 increased risk of dementia and cognitive dysfunction (3). With metabolic syndrome (MetS) considered
5 a precursor of type 2 diabetes (4) and central obesity and insulin resistance (IR) being recognized as
6 important causative factors in the pathogenesis of MetS (5), a precursor state for dementia may be
7 developed over several years.

8 The long prodromal phases characterizing dementia and type 2 diabetes challenges the study of
9 potential risk factors and their temporal relation (6,7) and in studies with short follow-up, putative
10 relationships may be unreliable. Thus, reported associations between type 2 diabetes, MetS, and
11 cognitive dysfunction are somewhat contrary. Until recently the brain was considered an insulin
12 insensitive organ, it has however now been accepted that insulin, partly of peripheral origin, acts
13 through its own receptors in the brain controlling cognition and memory(8). Thus it may be that IR is a
14 condition affecting both peripheral and central insulin receptors with cerebral IR being part of a
15 preclinical state of Alzheimer's disease(9). Importantly, the temporal relation between MetS, IR, and
16 cognitive dysfunction/dementia has recently been questioned (10,11). This prompted us to conduct the
17 current study in which data obtained as part of The Prospective Epidemiological Risk Factor (PERF)
18 study, a prospective study of Danish postmenopausal women (12), underwent an evaluation with the
19 aim to study the hypothesis that there is a temporal relation between MetS and IR and cognitive
20 dysfunction. Data from PERF were used to evaluate whether there is an association between the MetS
21 or IR and cognitive impairment at a follow-up 15 years later including only subjects without signs of
22 cognitive dysfunction at the baseline examination (n = 1759).

23

1 **Research design and Methods**

2 *The Prospective Epidemiological Risk Factor Study*

3 The Prospective Epidemiological Risk Factor (PERF) Study, an observational, prospective cohort study
4 of Danish postmenopausal women, was designed with the purpose to obtain knowledge of age-related
5 diseases in postmenopausal women. The baseline examination (PERF I) took place between 1999 and
6 2001 (n=5,855) and over fourteen months (from September 2013) 2,103 participants were included in a
7 follow-up (PERF II) as described previously (12). The studies were carried out in accordance with
8 ICH-GCP with study protocol approval from The Research Ethics Committee of Copenhagen County.
9 Written informed consent was obtained from all subjects prior to any study related procedures.

10 *Study populations*

11 This study was based on all subjects that completed the follow-up examination, PERF II (n = 2,103)
12 and from this population we identified the analytical sample as outlined in figure 1.

13 (figure 1 here)

14 The study population included all subjects with valid cognitive tests at baseline and follow-up.

15 Exclusion criteria were cognitive dysfunction at baseline and missing data on any of the confounders
16 included in the analysis. This qualified 1,759 subjects for the analysis.

17 *Cognitive dysfunction*

18 Two short cognitive screening tests were applied to assess cognitive function at baseline and follow-up.

19 The Short Blessed Test (SBT) is a six-item test assessing orientation, concentration, and memory. The
20 score ranges from 0 to 28, with lower scores indicating better performance. A threshold of ≥ 10 was

1 previously identified as cognitive impairment consistent with dementia (13). The category fluency test
2 with animal naming (CFT) is a measure of verbal fluency where the subjects should name as many
3 animals as possible in 60 seconds. Higher scores indicate better performance and the recommended
4 threshold for dementia is ≤ 14 (14).

5 *Metabolic Syndrome at baseline*

6 MetS was defined using a modified version of the definition recommended by the International
7 Diabetes Federation(15). Beside the entrance criteria of central obesity subjects should present two or
8 more of the following risk factors: Increased triglycerides (>1.7 mmol/L), lowered level of HDL
9 cholesterol (<1.29 mmol/L), an increase in fasting plasma glucose (>5.6 mmol/L) or previously
10 diagnosed type 2 diabetes, hypertension (systolic pressure above 130 mmHg or diastolic pressure
11 higher than 85 mmHg or existing treatment of hypertension) to qualify for MetS. A direct measure of
12 waist circumference was not obtained at baseline and therefore, the entrance criteria of central obesity
13 was only defined by a BMI above 30 kg/m² and as specific hyperlipidemia treatment was not part of
14 the baseline questionnaire, we are unable to determine whether participants were on specific lipid-
15 lowering medication.

16 Subjects without MetS were divided into three groups: *i*) subjects having a BMI >30 kg/m², and only
17 one additional risk factor; *ii*) subjects presenting BMI <30 kg/m² but with 1-4 risk factors for MetS; and
18 *iii*) subjects without any risk factors for MetS. This group was used as the reference group in the
19 regression analysis.

20 *The homeostasis model assessment index*

The homeostasis model assessment index (HOMA-IR) index was used to assess the degree of IR (16). The HOMA-IR index was calculated by fasting levels of plasma glucose multiplied by the concentration of insulin divided by the constant 22.5. Fasting plasma glucose was measured directly after collection in both PERF I and II, using a Vitros 250 slide cartridge with no reagent system from Ortho Clinical, in PERF I, and an enzymatic measurement method using the Avida 1800, from Siemens, in PERF II. Insulin levels at PERF I and PERF II was measured in thawed samples from the PERF biobank (stored at -80°C) on a Cobas e411 analyser from Roche. Blood samples were collected fasting in the morning.

Statistical analysis

Statistical analysis was conducted using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Spearman's Rank-Order Correlation was used to measure the association between scores of the two cognitive tests. By use of the *glm* function, logistic regression assessed the association between risk factors for the MetS, metabolic profiles and cognitive dysfunction. Three separate multivariable analyses were completed. In all analyses, baseline age and baseline cognitive performance were included as continuous variable and education level (primary school/high school/university), smoking history (never/former/current), alcohol consumption (none/<10.5 alcohol units per week/10.5-21 alcohol units per week/>21 alcohol units per week) and physical activity (Inactive/1 time per Week/2 times per Week/3+ times per week) and current use of hormone replacement therapy (yes/no) as categorical covariates.

We first tested each of the single risk factors comprising the MetS. The variables were dichotomized as described under “*Metabolic Syndrome at baseline*” above. Using the dichotomized variables we then studied how metabolic profiles at baseline were associated with cognitive dysfunction. First, we used

1 the modified definition of MetS followed by the cumulative sum of MetS risk factors, ranging from
2 zero to five, then we assessed the association between IR and risk of cognitive dysfunction. The
3 baseline HOMA-IR index was used as continuous variable and further dichotomized at 2.6, where
4 subjects above the threshold was considered insulin resistant. The outcome variables used were *i*)
5 cognitive dysfunction on the SBT ($SBT \geq 10$), *ii*) cognitive dysfunction on the CFT ($CFT \leq 14$), and *iii*)
6 cognitive dysfunction on both SBT and CFT ($SBT \geq 10$ and $CFT \leq 14$).
7 The Hosmer-Lemeshow test was used to test the goodness of fit for the logistic regression models.

8 **Results**

9 Of the 1,759 subjects included in the analysis, 136 had cognitive dysfunction according to the SBT,
10 while 326 were classified with cognitive dysfunction when it was determined by CFT. A total of 80
11 subjects showed signs of cognitive dysfunction on both tests.

12 *Characteristics of the study population*

13 The baseline characteristics of the study population is shown in table 1. All subjects were on average
14 68 years old at baseline, with the non-impaired group as the youngest and the group of subjects with
15 impaired cognition on both tests as the oldest.

16 (table 1 here)

17 There was a negative correlation between scores in the SBT and the CFT ($\rho = -0.294$ [-0,336 to -
18 0,250], $p < 0.0001$).

19 *The association between Metabolic Syndrome, Insulin resistance and cognitive dysfunction*

Table 2 shows the association between metabolic risk factors, MetS, IR and cognitive dysfunction at follow-up. Fasting plasma glucose was associated with impairment in CFT suggesting that hyperglycemia increases the risk for development of cognitive dysfunction with 44% (OR 1.44, 95% CI 1.09-1.91). Having from one to four metabolic risk factors did not significantly alter the risk of cognitive dysfunction at follow-up when compared to subjects with no risk factors. In subjects with the worst metabolic profile, holding all five risk factors for MetS, the risk for cognitive dysfunction on verbal fluency was three times higher (OR 3.09, 95% CI 1.09-8.69) as compared to subjects who did not present any of the MetS risk factors. MetS was however not associated with increased risk of cognitive dysfunction at follow-up.

(table 2 here)

IR was associated with an increased risk of cognitive dysfunction, calculated both as CFT and a combination of the SBT and the CFT (Table 2). The risk of cognitive dysfunction increased between 8-10% for every unit increase on the HOMA-IR index scale and when dichotomized, subjects above the threshold of 2.6 had a 47% higher risk of cognitive dysfunction on verbal fluency (OR 1.47, 95% CI 1.09-1.99) as compared to subjects below the HOMA-IR threshold.

1 **Discussion**

2 In the present study we assessed the temporal relation between biomarkers and precursors of type 2
3 diabetes and cognitive dysfunction and specifically we evaluated whether MetS and IR are associated
4 with development of cognitive dysfunction. Based on data with a follow-up period of up to 15 years it
5 is demonstrated that *i)* subjects with impaired fasting plasma glucose have larger odds of developing
6 cognitive dysfunction and *ii)* subjects with IR as determined by the HOMA-IR index have higher
7 probability of developing cognitive dysfunction. While fasting plasma glucose were specifically
8 associated with dysfunction on the verbal fluency test, IR seemed to result in more global cognitive
9 dysfunction as determined by a combination of two short cognitive screening tests. The third important
10 finding is that subjects with a poor metabolic profile, reflected by the presence of several metabolic and
11 cardiovascular risk factors, have a 3- to 4-fold larger odds of developing cognitive dysfunction than
12 subjects with an ideal metabolic profile. Overall the data suggest that IR is a cause rather than a
13 consequence of cognitive dysfunction.

14 Fasting plasma glucose was the single metabolic risk factor that was most strongly associated with
15 cognitive dysfunction. With cognitive function assessed by the CFT, subjects with impaired fasting
16 plasma glucose levels had a 44% (9%-91%) larger odds of cognitive dysfunction as compared to
17 normoglycemic subjects. While presence of MetS in itself does not seem to provoke an elevated risk of
18 cognitive dysfunction, subjects with a poor metabolic profile have a three to four time's larger odds of
19 developing cognitive dysfunction when compared to subjects with an ideal metabolic profile. The
20 Framingham cohort have recently shown that subjects with ideal cardiovascular health, determined
21 from a 7-point scale proposed by the American Heart Association, are at lower risk of dementia,
22 cognitive decline and brain atrophy(17). Out of the seven risk factors defining an ideal cardiovascular

health profile, four is identical or at least very similar to those defining the MetS, suggesting that cardiovascular and metabolic health is closely linked to brain health.

Peripheral IR has been shown to alter the transport of insulin through the blood-brain barrier. The insulin transport is reduced by peripheral hyperinsulinemia (18), which can directly contribute to cognitive impairment and promote AD pathology(19,20). It has also recently been shown that IR predicts worse memory performance through a reduction in regional cerebral glucose metabolism (21), supporting IR being a causal risk factor for development of cognitive dysfunction. While the study design does not allow for causal conclusions, the data presented here can be taken to indicate a temporal relation between IR and cognitive dysfunction. However, we cannot rule out the possibility that dementia or cognitive dysfunction leads to a diabetic phenotype and that a disturbance in insulin homeostasis, as a secondary process, may accelerate certain dementia pathologies (22). IR may be a shared underlying pathological mechanism, since it is part of the prodromal phase of both type 2 diabetes and dementia. Interestingly amyloid formation is a pathological hallmark of both type 2 diabetes and AD: islet amyloid polypeptide is found in the pancreas of subjects with type 2 diabetes and β -amyloid is in the brain of subjects with AD (23). A recent study even suggest that pancreatic derived amyloid may enter the brain and exacerbate the disposition of β -amyloid through cross-seeding (24).

There are previous studies indicating an association between sleep disturbances and dementia (25). Mechanisms underlying the association are many, and IR is speculated to play an important role, however the causal link has not been elucidated. The menopausal transition is associated with sleep disturbances, which are also found to increase the risk of type 2 diabetes (26,27). As we observed a link between IR and cognitive dysfunction, it could indicate that IR is an intermediate mechanism for the

1 causal association between sleep disturbances and cognitive dysfunction. We can however not address
2 this in the current study as we did not collect information on sleep disturbances and sleep patterns at
3 baseline.

4 The small, albeit significant, correlation between the two tests was expected and indicate that the two
5 tests are not equivalent. This was reflected in the observed domain-specific effect of fasting plasma
6 glucose and IR on cognition specifically related to verbal fluency. A similar domain-specific effect on
7 verbal fluency has previously been found in two cross-sectional studies (28,29). One of the studies
8 found that the effect of IR on cognition was modulated by gender, indicating that IR was associated
9 with poor performance on verbal fluency only in women. Verbal fluency performance is functionally
10 linked to the frontal and temporal lobe areas. These brain areas rich in insulin receptors, are found to be
11 associated with memory function(28,30). There are several neuropathological conditions that affect
12 memory-related areas in the brain, with AD being one of them. A structural alteration of semantic
13 networks located in the frontal and temporal lobe areas has been found to be characteristic for AD even
14 in the early stages of AD (31,32).

15 The concept of precision medicine is emerging in relation to prevention and treatment of AD (33) and
16 the abundant evidence of various AD phenotypes, the metabolic phenotype being one, suggests that it
17 is extremely relevant in this field. A recent meta-analysis indicate that insulin sensitizer drugs, like
18 metformin and thiazolinediones, might be useful in the prevention of dementia in diabetic patients (34).
19 Whether there is a direct mechanistic link is still controversial, but evidence from rat studies have
20 shown that the glucagon-like peptide 1 analog liraglutide, another insulin sensitizer, interacts directly
21 with processes leading to amyloid plaques and neurofibrillary tangles, the two pathological hallmarks
22 of AD (35,36). Moreover, clinical trials have shown promising effects of intranasal insulin in subjects

1 with AD and its prodrome, mild cognitive impairment (37,38) and also on spatial memory in young
2 men (39).

3 The analysis was restricted to subjects attending the follow-up examination, therefore selection bias
4 may affect the internal validity and question the generalizability of our results as it is well-known that
5 cognitive dysfunction and dementia affect attrition. We have previously assessed the similarities
6 between follow-up participants and follow-up non-participants on a cohort level, and found that the two
7 populations are very similar (12). This should strengthen the internal validity. Further, we based our
8 determination of cognitive dysfunction on two short cognitive screening tools at the follow-up visit,
9 therefore we cannot not rule out the possibility that cognitive dysfunction in the current study may be
10 caused by reversible conditions and thereby potentially result in misclassification. The diagnostic
11 accuracy of the two tests in relation to dementia is excellent (40–43). They have even been shown to
12 outperform more comprehensive tests like the Mini Mental State Examination in the identification of
13 milder levels of impairment (44,45). In the absence of a comprehensive diagnostic workup with a
14 complete neuropsychological test battery, this evidence support the use of these simple tests.

15 Another limitation is the lack of repeated measurement of glucose, insulin and cognition throughout the
16 follow-up period as it would allow for a better assessment of the mutual trajectories and also resulted in
17 a more accurate determination of the onset of cognitive dysfunction. Given the previously reported
18 interconnection between genetic and metabolic risk factors, the lack of genetic risk factors in our
19 studies is a limitation that could result in unmeasured confounding. For example it has been suggested
20 that the insulin metabolism may differ between Apolipoprotein E epsilon 4 allele carriers and non-
21 carriers (46).

1 **Conclusion**

2 The precursors of type 2 diabetes; impaired fasting plasma glucose and IR, are associated with
3 increased risk of developing cognitive dysfunction in elder women. Moreover, subjects with a poor
4 metabolic profile are more likely to develop cognitive dysfunction than subjects with an ideal
5 metabolic profile. If the observed association between metabolic risk factors and cognitive dysfunction
6 is truly causal it could suggest that a significant proportion of dementia cases in women may be
7 preventable by effective control of insulin homeostasis.

8

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2 KH is the guarantor of this work and, as such, had full access to all the data in the study and takes
3 responsibility for the integrity of the data and the accuracy of the data analysis

4 *Author contributions*

5 JSN: wrote the manuscript, performed the literature search, data and statistical analysis, data
6 interpretation. KD: reviewed and revised the manuscript, supported data interpretation and statistical
7 analysis CC: contributed to the study design, acquired data and gave scientific advice. MAK: reviewed,
8 and revised the manuscript including data interpretation and scientific advice. HBN and SB: reviewed
9 and revised the manuscript KH: reviewed and revised the manuscript, supported data interpretation and
10 gave scientific advice. All authors approved the final version of the manuscript.

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15 *Conflicts of Interest*

16 JSN, KD and SB reports no disclosures. CC serves as board member and stock owner in Nordic
17 Bioscience A/S. HBN are full-time employee of ProScion A/S. MAK and KH are full-time employees
18 of and hold stocks in Nordic Bioscience A/S.

19

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1 Tables

2 **Table 1: Baseline characteristics of the study population.** Numbers are shown as absolute numbers
 3 with percentile in brackets for categorical variables. For numerical variables the mean \pm standard
 4 deviation (SD) are shown.

Variable	Non	SBT ≥ 10		
	impaired n = 1377	SBT ≥ 10 n = 136	CFT ≤ 14 n = 326	CFT ≤ 14 n = 80
Demographics				
Age (years)	66.9 \pm 5.6	70.6 \pm 6.5	70.5 \pm 5.8	72.4 \pm 5.7
Education: Primary school, n (%)	903 (65.6)	96 (70.6)	225 (69.0)	56 (70.0)
High School, n (%)	332 (24.1)	26 (19.1)	77 (23.6)	17 (21.2)
University, n (%)	142 (10.3)	14 (8.1)	24 (7.4)	7 (8.8)
Lifestyle				
BMI (kg/m ²)	26.0 \pm 4.0	26.3 \pm 4.8	26.5 \pm 4.4	26.3 \pm 4.3
<18,5, n (%)	19 (1.2)	1 (0.7)	2 (0.6)	0
18,5-24,9, n (%)	686 (42.3)	63 (46.3)	133 (40.8)	36 (45.0)
25,0-29,9, n (%)	653 (40.2)	46 (33.8)	127 (39.0)	28 (35.0)
$\geq 30,0$, n (%)	265 (16.3)	26 (19.1)	64 (19.6)	16 (20.0)
Smoking History: Never, n (%)	723 (52.5)	68 (50.0)	167 (51.2)	45 (56.2)
Former, n (%)	403 (29.3)	41 (30.1)	89 (27.3)	23 (28.7)
Current, n (%)	251 (18.2)	27 (19.9)	70 (21.5)	12 (15.0)
Alcohol: None, n (%)	512 (37.2)	66 (48.5)	148 (45.4)	36 (45.0)
<10.5 alcohol units/week, n (%)	312 (22.7)	22 (16.2)	61 (18.7)	15 (18.8)
10.5–21 alcohol units/week, n (%)	423 (30.7)	38 (27.9)	89 (27.3)	22 (27.5)
>21 alcohol units/week, n (%)	130 (9.4)	10 (7.4)	28 (8.6)	7 (8.8)

Physical activity: Inactive, n (%)	306 (22.2)	40 (29.4)	103 (31.6)	22 (27.5)
1 time /week, n (%)	310 (22.5)	29 (21.3)	54 (16.6)	17 (21.2)
2 times/week, n (%)	204 (14.8)	18 (13.2)	48 (14.7)	11 (13.8)
3+ times/week, n (%)	557 (40.5)	49 (36.0)	697 (37.1)	30 (37.5)
Metabolic and Vascular factors				
Systolic Blood Pressure (mmHg)	145.5 ± 23.1	148.9 ± 23.7	148.8 ± 23.2	150.2 ± 23.9
Diastolic Blood Pressure (mmHg)	81.9 ± 10.5	82.0 ± 10.5	82.0 ± 11.0	81.5 ± 10.8
Fasting Plasma Glucose (mmol/L)	5.4 ± 1.0	5.6 ± 1.5	5.6 ± 1.1	5.8 ± 1.8
Insulin (mmol/L)	54.9 ± 34.6	58.7 ± 44.5	60.9 ± 38.8	61.5 ± 42.1
HOMA-IR	2.0 ± 1.5	2.4 ± 3.6	2.3 ± 2.6	2.6 ± 4.3
High density lipoprotein (mmol/L)	1.7 ± 0.4	1.7 ± 0.4	1.8 ± 0.5	1.8 ± 0.4
Triglycerides (mmol/L)	1.3 ± 0.6	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.7
Cognitive performance				
Short Blessed Test	1.3 ± 1.9	2.4 ± 2.4	1.7 ± 2.1	2.4 ± 2.3
Category Fluency Test	24.3 ± 5.2	21.5 ± 4.5	20.6 ± 4.2	20.8 ± 4.4

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1 **Table 2: Association between Metabolic Syndrome, Insulin resistance and cognitive dysfunction**

Predictor variables	Cognitive status at follow up					
					SBT ≥10 &	
	SBT ≥10		CFT ≤14		CFT≤14	
	OR*	95% CI	OR*	95% CI	OR*	95% CI
Individual Component of the MetS						
Body Mass Index (>30kg/m2)	1.22	0.76 - 1.94	1.24	0.88 - 1.74	1.26	0.70 - 2.30
Elevated Blood Pressure	0.88	0.56 - 1.38	1.07	0.76 - 1.50	0.68	0.38 - 1.23
Impaired Fasting Plasma Glucose	1.12	0.76 - 1.64	1.44	1.09 - 1.91	1.56	0.96 - 2.52
Low High Density Lipoprotein	1.01	0.59 - 1.74	1.19	0.81 - 1.74	0.99	0.47 - 2.09
Elevated Triglycerides	1.25	0.81 - 1.91	0.98	0.71 - 1.36	1.09	0.61 - 1.95
Cumulative sum of risk factors for MetS						
0 risk factors	reference					
1 "	0.72	0.40 - 1.27	1.02	0.65 - 1.59	0.72	0.34 - 1.56
2 "	0.64	0.35 - 1.19	1.06	0.66 - 1.69	0.60	0.27 - 1.38
3 "	1.18	0.61 - 2.27	1.19	0.70 - 2.03	1.02	0.41 - 2.52
4 "	0.59	0.22 - 1.60	1.39	0.71 - 2.71	0.66	0.19 - 2.33
5 "	2.56	0.75 - 8.79	3.07	1.09 - 8.69	4.35	1.02 - 18.6
Metabolic Syndrome						
No MetS	reference					
Risk factors for MetS with BMI < 30 kg/m2	0.98	0.65 - 1.49	1.08	0.80 - 1.46	0.94	0.55 - 1.61
BMI >30kg/m2 and < 2 risk factors	1.11	0.53 - 2.33	1.30	0.77 - 2.19	1.61	0.69 - 3.77
Metabolic Syndrome	1.28	0.71 - 2.29	1.30	0.82 - 1.94	1.18	0.55 - 2.55
Insulin Resistance (HOMA-IR)						
Dichotomized (HOMA-IR > 2.6)	0.98	0.64 - 1.52	1.47	1.09 - 1.99	1.33	0.77 - 2.27

Continuous (per unit increase)	1.05	0.98 - 1.13	1.08	1.01 - 1.16	1.10	1.01 - 1.19
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*Odds ratios were adjusted for Age at Baseline, Smoking history, Alcohol Consumption, Physical Activity, Education and Hormone replacement therapy

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1 **Figure legends**

2 Figure 1: Flowchart for the identification of the analytical sample. Each outcome was determined
3 independent of the other outcomes. SBT: Short Blessed Test, CFT: Category Fluency test.

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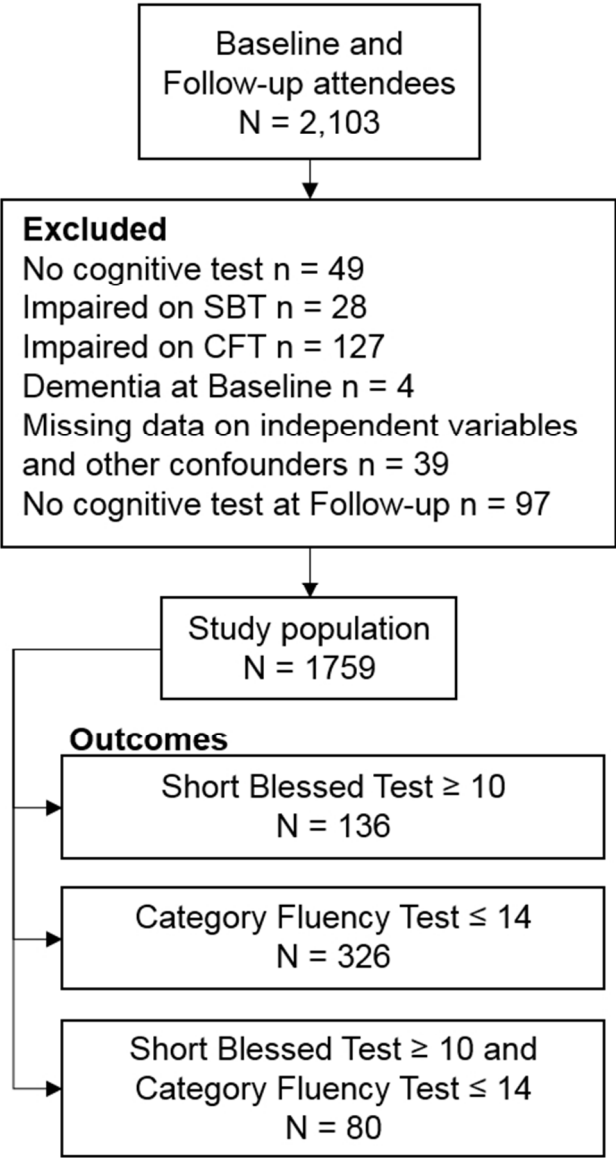


Figure 1: Flowchart for the identification of the analytical sample. Each outcome was determined independent of the other outcomes. SBT: Short Blessed Test, CFT: Category Fluency test.
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